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protein with the protein product of bacteriophage gene VIII can be found, for example, in pending claim 8. Support for the amendment to claim 1 to recite that the cells are prokaryotic cells and that the first and second DNA sequences are contained in vectors can be found, for example, in claim 76 and at page 6, lines 24-26. Support for the amendment to claim 16 to recite that the DNA sequence between each pair of restriction sites in the two vectors is homologous enough to allow annealing can be found, for example, at page 9, line 34, to page 10, line 1. Support for the amendment to claim 26 to recite that the first or second DNA sequence is operatively linked to bacteriophage gene VIII can be found, for example, in pending claim 33. Additional amendments to claim 26 have been made for clarity. The amendments to claims 7, 28 and 32 have been made to provide appropriate antecedent basis. Accordingly, the amendments do not introduce new matter or raise new issues for consideration, and entry thereof is respectfully requested.

Rejections under 35 U.S.C. § 101

Claims 1, 3-5 and 80 remain rejected under 35 U.S.C. § 101 as allegedly encompassing non-statutory subject matter. The Office Action maintains that receptors from the immunoglobulin superfamily are "fusion proteins" and, therefore, the claims encompass immune cells as they occur in nature. Applicant notes that claim 80 is no longer pending. Therefore, the rejection will be addressed as it applies to claims 1 and 3-5.

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Applicant maintains, for the reasons of record, that immunoglobulin superfamily members as they occur in nature are not "fusion proteins." Nevertheless, claim 1 has been amended above to recite that the cells are prokaryotic cells, and that one or both of the encoded polypeptides are expressed as a fusion protein with the protein product of bacteriophage gene VIII. As such, claims 1 and 3-5 clearly do not encompass lymphocytes as they occur in nature and, therefore, Applicants respectfully request that the rejection of claims 1 and 3-5 under 35 U.S.C. § 101 be removed.

Claims 7, 8 and 77 also stand rejected under 35 U.S.C. § 101 as allegedly directed to a non-functional invention due to the plurality of cells being required to produce bacteriophage without limiting the cells to bacterial cells. Although Applicant maintains that the invention as claimed is functional, claim 1 has nevertheless been amended to recite that the cells are prokaryotic cells, and claim 8 has been canceled. Therefore, Applicant submits that the claims as amended above are directed to a functional invention, and respectfully requests that rejection of claims 7, 8 and 77 under 35 U.S.C. § 101 be removed.

Double-patenting rejections

Claims 1-33 and 68-75 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-33 and 68-75 of copending application serial number 08/470,297. Claims 1-8 and 16-33 stand provisionally rejected under the judicially created doctrine of obviousness-type double

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patenting as allegedly unpatentable over claims 1-8, 16-21 and 23-33 of application serial number 08/349,131. Applicant wishes to draw the Examiner's attention to the issuance of application serial number 08/349,131 as U.S. Patent No. 5,871,974. Applicant respectfully requests that these grounds of rejection be deferred until there is an indication of allowable subject matter in the subject application.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, 8, 16-33 and 66-77 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that the pending claims do not currently reflect those elements which the specification identifies as the inventive contribution of Applicant.

In regard to claim 1, the Office Action alleges that the claim does not reflect Applicant's inventive contribution of providing a system of two vectors which only form proper combinations of first and second DNAs.

Applicant submits that claim 1 adequately reflects Applicant's inventive contribution. One embodiment of Applicant's invention is the expression of heteromeric receptors on the surface of prokaryotic cells where one or both of the heteromeric receptor subunits is expressed as a fusion protein with gene VIII (see, for example, page 3, lines 5-12). Given the teachings in the specification, the prokaryotic cells expressing heteromeric receptors on their surface as gene VIII fusion

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proteins can be generated using essentially any compatible vector/host system, as described at page 6, lines 24-34 of the specification. Such prokaryotic cells do not require a system of two vectors which only form proper combinations of first and second DNAs. The plurality of prokaryotic cells recited in claim 1 is directed to this embodiment and is sufficiently enabled by the specification to allow one skilled in the art to practice the invention as claimed. In another embodiment, the plurality of prokaryotic cells expressing heteromeric receptors on their surface as gene VIII fusion proteins can also be generated using the described vector system which forms proper combinations of first and second DNAs. Although not necessary to practice the invention as claimed, this vector system provides certain advantages, such as large population size and diversity (page 4, lines 15-19).

As amended above, claim 1 indicates that the DNA sequences are contained in vectors, and that the protein to which one or both of the polypeptides is fused is the gene VIII protein of a filamentous bacteriophage. The cells of claim 1 can advantageously be used to screen heteromeric receptors expressed on the surface of a cell (see, for example, page 4, lines 19-21).

The specification teaches, at page 6, lines 20-30, that expression of a heteromeric receptor on the surface of a cell can be performed in any compatible vector/host system. The specification exemplifies a two vector system that advantageously provides for the operative combination of vector portions containing the first and second DNA sequences encoding

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heteromeric receptors (see, for example, page 7, line 1, to page 11, line 9). However, given the teachings in the specification, Applicant maintains that those skilled in the art would have been able to make and use the cells of claim 1 with regard to any suitable vector that contains first and second DNA sequences encoding first and second polypeptides which form heteromeric receptors, wherein one or both of the polypeptides is expressed as a fusion protein with the protein product of bacteriophage gene VIII.

In regard to claim 16, the Office Action states that a claim must not only recite elements that distinguish the claimed invention from the art, but must also recite sufficient elements to produce an invention that works. The Office Action alleges at page 4, lines 2-6, that "simply incorporating a DNA encoding a protein between two pairs of symmetrically oriented restriction sites in a vector which is otherwise unrelated to a second vector containing a DNA encoding a protein wherein the second DNA is located between those same two restriction sites in opposite orientation will not facilitate the joining of only the coding portions of those two vectors into a single vector."

Applicants maintain, for the reasons of record, that claim 16 recites a novel, unobvious and useful invention. Nevertheless, as amended above, claim 16 indicates that the DNA between the two restriction sites in the first pair of restriction sites in the two vectors is homologous enough to allow annealing, and the DNA between the two restriction sites in the second pair of restriction sites in the two vectors is

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homologous enough to allow annealing (see page 9, line 32, to page 10, line 1 of the specification). The additional element recited in claim 16, as amended, provides the advantages taught in the specification of allowing operative combination of only those vector portions that provide for the coexpression of the DNA sequences inserted into the cloning sites.

The specification teaches how to operatively combine the two vectors of claim 16 so that only proper combinations of vector portions are randomly brought together (see, for example, page 9, line 32, to page 10, line 5; page 10, line 34, to page 11, line 3; and page 32, lines 6-20). Operative combination of the vectors can be accomplished, for example, by restricting each of the vectors of the kit with a restriction enzyme that cleaves the distal restriction site in each pair with respect to the cloning site. When the DNA sequences between the pairs of restriction sites are made single stranded, the restricted vector populations can be mixed and the homologous sequences annealed, such that the appropriate portions of the two vectors will be operatively combined through the two pairs of restriction sites to form a single vector for the coexpression of the DNA sequences cloned into the cloning sites.

In regard to claim 26, directed to a plurality of expression vectors containing first and second DNA sequences that encode first and second polypeptides of a heteromeric receptor, Applicants maintain, for the reasons of record, that claim 26 is sufficiently enabled by the specification, which teaches how to make and use the plurality of vectors. Nevertheless, claim 26

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has been amended above to recite that the first or second DNA sequence is operatively linked to bacteriophage gene VIII. Claim 26 has also been amended to more specifically indicate that each of the vectors in the plurality contains a first and second DNA sequence.

Claims 7, 8 and 77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because the specification does not provide the guidance to produce bacteriophage in a cell that is not bacterial.

Although Applicant maintains that the invention as claimed is enabled, claim 8 has nevertheless been canceled, and claim 77 has been amended to depend on claim 76, which is directed to prokaryotic cells. Therefore, Applicant submits that it is clear that the filamentous bacteriophage are produced by prokaryotic cells and, accordingly, respectfully requests that this ground of rejection be removed.

In view of the above remarks, Applicants respectfully submit that claims 1 to 5, 7, 8, 16 to 33 and 66 to 77 are sufficiently enabled by the specification and, therefore, request that the rejection under 35 U.S.C. § 112, first paragraph, be removed.

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Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-5, 7, 8, 16-33 and 66-77 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office Action alleges that the claims are incomplete for omitting essential elements.

As described above in response to rejections under 35 U.S.C. § 112, first paragraph, the text of which is incorporated herein by reference, claim 1 has been amended above to indicate that the cells contain vectors, and that one of the polypeptides is expressed as a fusion with the protein product of bacteriophage gene VIII; claim 16 has been amended above to indicate that the DNA between the two restriction sites in the first pair of restriction sites in the two vectors is homologous enough to allow annealing, and the DNA between the two restriction sites in the second pair of restriction sites in the two vectors is homologous enough to allow annealing; and claim 26 has been amended above to indicate that the first or second DNA sequence is operatively linked to bacteriophage gene VIII. Applicant respectfully submits that the claims, as amended, contain the necessary elements for the practice of the invention and are thus sufficiently clear and definite.

Claims 7, 26 to 33 and 77 stand rejected as allegedly incomplete for omitting essential structural cooperative relationships of elements.

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As stated above, claim 77, on which claim 7 depends, has been amended to depend on claim 76, which is directed to prokaryotic cells. Therefore, Applicant submits that the structural relationship between claims 7 and 77 is sufficiently clear.

The Office Action alleges that claim 26 is confusing because it is unclear if each of the plurality of expression vectors is supposed to contain a first and second DNA sequence, or if the first and second DNA sequences are to be encoded by separate vectors.

Although Applicant maintains that claim 26 is sufficiently clear and definite, claim 26 has nevertheless been amended above to more particularly indicate that each of the vectors in the plurality of expression vectors contains a first and a second DNA sequence encoding a first and second polypeptide. Additional amendments have been made to claim 26 for clarity, and to indicate that the first or second DNA sequence is operatively linked to bacteriophage gene VIII.

In view of the above remarks, Applicant submits that the claims are sufficiently clear and definite, and respectfully requests that the rejection of claims 1-5, 7, 8, 16-33 and 66-77 under 35 U.S.C. § 112, second paragraph, be removed.

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Rejections under 35 U.S.C. § 103

Claims 1-5 and 25-30 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Huse et al., Science 246:1275-1281 (1989), in view of Ladner et al. (WO 88/06630). The Office Action alleges that the instant claims differ from the Huse et al. reference in that the receptor protein of Huse et al. is confined to the host cell cytoplasm, whereas the receptor protein of the instant invention is expressed on the cell surface. Ladner et al. is alleged to provide motivation to express a binding protein on the surface of the cell.

Although Applicant maintains, for the reasons of record, that the combination of Huse or Ladner does not teach or suggest expressing two polypeptides at the surface of a cell to produce a heteromeric receptor, nevertheless claim 1 has been amended above to recite that the polypeptide is expressed as a fusion protein with the protein product of bacteriophage gene VIII, and claim 26 has been amended above to recite that the first or second DNA sequence is operatively linked to bacteriophage gene VIII.

Applicant respectfully submits that neither Huse nor Ladner teaches or suggests expressing a first and second polypeptide as a fusion protein with bacteriophage gene VIII protein on the surface of a cell. More specifically, Applicant maintains, for the reasons of record, that Huse et al. describes the expression of antibody libraries in the host cell cytoplasm, and does not teach or suggest expression of heteromeric receptors

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on the surface of a cell. Ladner et al. describes the expression of single chain antibodies as fusion proteins with lambda gene V, and does not teach or suggest co-expressing two independent polypeptides for their assembly on the surface of a cell to form a heteromeric receptor. Additionally, neither publication, alone or in combination, teaches or suggests fusing one or both heteromeric polypeptide subunits to a filamentous bacteriophage gene VIII protein for expression on the surface of a cell. Therefore, Applicant respectfully submits that the combination of Huse and Ladner cannot teach or suggest Applicant's claimed invention.

Claims 6-8, 22-24 and 31-33 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Huse et al. and Ladner et al., as applied to claims 1-5 and 25-30 above, and further in view of Parmley et al. The Office Action cites Parmley et al. as allegedly showing that the use of a filamentous bacteriophage vector to obtain the surface expression of a potential binding protein on the surface of a bacteriophage was a practice known in the art prior to the making of the instant invention.

In regard to claims 22-25, Applicant points out that these claims depend from claim 16, which is directed to a cloning system for the coexpression of two or more DNA sequences encoding polypeptides which form heteromeric receptors. Applicant maintains that none of the cited art has been applied to claim 16 and, therefore, dependent claims 22-25 are also unobvious over the cited art.

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In regard to claims 6-8 and 31-33, Applicant maintains, for the reasons of record, that Parmley et al. does not provide that which is lacking in the combination of Huse et al. and Ladner et al. More specifically, Applicant maintains that Parmley et al. does not teach or suggest the expression of two polypeptide subunits that form heteromeric receptors on the surface of a cell. Furthermore, Parmley et al. does not teach or suggest fusing a receptor subunit to a bacteriophage gene VIII polypeptide for expression on the surface of a cell. Applicant maintains, therefore, that Parmley et al. cannot be combined with Huse et al. and Ladner et al. to arrive at Applicant's claimed invention.

Claims 1 to 5 and 25 to 30 also remain rejected under 35 U.S.C. § 103 as allegedly obvious over Sastry et al., Proc. Natl. Acad. Sci. 86:5728-5732 (1989), in view of Ladner et al. (WO 88/06630) and Robinson et al. (WO 87/02671).

Applicant maintains, for the reasons of record, that neither Sastry et al. nor Robinson et al. teaches or suggests expressing two polypeptides that form a heteromeric receptor on the surface of a cell. As described above, Ladner et al. does not teach or suggest expressing two polypeptides separately as a first and second polypeptide to form a heteromeric receptor on the surface of a cell. Furthermore, none of the cited references, either alone or in combination, teaches or suggests fusing one or both heteromeric polypeptide subunits to a bacteriophage gene VIII for expression on the surface of a cell. Therefore, Applicant respectfully submits that the combination of

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Sastry, Robinson and Ladner cannot teach or suggest Applicant's claimed invention.

Claims 6-8, 22-24 and 31-33 also remain rejected under 35 U.S.C. § 103 as allegedly obvious over Sastry et al., Ladner et al., and Robinson et al., as applied to claims 1-5 and 25-30, and further in view of Parmley et al.

In regard to claims 22-25, Applicant again points out that these claims depend from claim 16, which is directed to a cloning system for the coexpression of two or more DNA sequences encoding polypeptides which form heteromeric receptors. Applicant maintains that none of the cited art has been applied to claim 16 and, therefore, dependent claims 22-25 are also unobvious over the cited art.

In regard to claims 6-8 and 31-33, Applicant maintains, for the reasons of record, that Parmley et al. does not provide that which is lacking in the Sastry et al., Robinson et al., and Ladner et al. references. More specifically, Applicant maintains that Parmley et al. does not teach or suggest the expression of two polypeptide subunits that form heteromeric receptors on the surface of a cell. Furthermore, Parmley et al. does not teach or suggest fusing a heteromeric receptor subunit to bacteriophage gene VIII for expression on the surface of a cell. Applicant submits, therefore, that Parmley et al. cannot be combined with Sastry et al., Robinson et al. and Ladner et al. to arrive at Applicant's claimed invention.

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In view of the above remarks, Applicant respectfully requests that the rejection of claims 1-8 and 22-33 under 35 U.S.C. § 103, be removed.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,



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